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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,856	12/04/2003	Manne Satyanarayana Reddy	BULK 3.0-034	8301

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EXAMINER	
CHENG, KAREN	
ART UNIT	PAPER NUMBER
1626	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/729,856	REDDY ET AL.	
	Examiner	Art Unit	
	Karen Cheng	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-88* is/are pending in the application.

4a) Of the above claim(s) *8-16 and 24-88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7 and 18-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-88 are pending in the instant application. Claims 1 and 17 have been cancelled by applicant. Claims 8-16 and 24-88 have been withdrawn from consideration.

Response to Amendment and Arguments

Applicant's amendments and arguments filed on 05/14/07 have been fully considered and entered into the application.

- The objections of claims 1-7 and 17-23 have been overcome by the amendment to the claims that delete "cetirizine" and insert its chemical name in place.
- The 35 USC 102(b) rejection of claims 1 and 17 have been overcome the cancellation of the claims.
- Applicant's arguments have overcome the 35 USC 112, 2nd paragraph rejections of claims 2, 4, 5, 18 and 20-21.

Applicant's arguments filed on 05/14/07 in regards to the following objections and rejections have been fully considered but they are not found persuasive.

- Applicant's arguments in regards to the 35 USC 112 2nd paragraph rejections of claims 2 and 18 for improperly referring to Figures 1 and 2 of the specification are not found persuasive. Applicant argues that incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances" and that X-ray diffraction patterns cannot be described in words, and reference to a figure is more concise than duplicating the patterns into the claims. However, as stated by MPEP § 2173.05(s),

incorporation by reference is a necessity doctrine, not for applicant's convenience. It is suggested that Applicant insert a copy of the Figure into the claims to overcome this rejection.

- Applicant's arguments in regards to the 35 USC 102(b) rejections of Claims 6 and 22 are not found persuasive. Applicant argues that Claim 6 and 22 have not been taught by Cossement *et al* (see UK Patent Application 2,225,321). However Cossement *et al* state that "the dihydrochloride of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid, also known by the generic name of cetirizine, has recently been introduced as a new medicament for the treatment of allergic syndromes" (on p.1, lines 12-15). Thus, Cossement *et al* teach that the dihydrochloride salt of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid is found in medicaments, otherwise known as pharmaceutical compositions.

- Applicant's arguments in regards to the 35 USC 112, 1st paragraph enablement rejections of Claims 6 and 22 are not found persuasive. Applicant argues that the specification shows that crystalline forms of the dihydrochloride salt of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid (hereafter referred to as cetirizine) are thermally stable and may be used as an active ingredient in pharmaceutical formulations. Additionally, applicant argues that the polymorphic forms do not have to be maintained and can be detected through X-ray powder diffraction techniques. However, it is well known that preparation of pharmaceutical compositions requires creating solutions, milling, adding diluents, excipients, surfactants, etc. An acceptable carrier for a pharmaceutical formulation can include water, or the

preparation process can include wet milling. Dissolving a specific crystalline form of a compound in water to form an aqueous solution would cause the compound to exist in free form rather than a crystalline form with an identifying X-ray diffraction pattern, and there is evidence to show that the compound would revert back to the claimed crystalline form. Applicant has not shown that the particular claimed form of the dihydrochloride salt of cetirizine is maintained in a pharmaceutical composition. Although the crystalline forms of the dihydrochloride salt of cetirizine are thermally stable when isolated, it cannot be said if in the process of preparing a pharmaceutical composition, the claimed crystalline form will be retained as the process of preparing a pharmaceutical composition will cause a specific crystalline form to convert back to the most thermodynamically stable form (i.e. the form with the lowest vapor pressure) (see Haleblian *et al*, p. 912).

Maintained Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims must stand alone to define the invention and incorporation into claims by express reference to the specification is not permitted. See Ex parte Fressola, 27 USPQ 2d 1608. Claims 2 and 18 improperly refer to the specification (e.g. Fig. 1, Fig. 2). This rejection can be overcome by inserting the figure into the claims.

New Claim Rejections - 35 USC § 112

Claims 6-7 and 22-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The nature of the invention

The nature of the invention is a pharmaceutical composition made with a crystalline form of levorotatory cetirizine dihydrochloride salt and dextrorotatory cetirizine and pharmaceutically acceptable excipients.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the preparation of compositions requires creating solutions, milling, adding diluents, excipients, lubricants, binders, disintegrating agents, etc (see p. 16 of specification for examples of excipients). The process of preparing a composition, such as a pharmaceutical composition containing a specific crystalline form is complex since polymorphs of a compound can arise when molecules of a compound stack in the solid state in distinct ways. Polymorphs tend to convert from less stable to more stable forms, and the rate of conversion depends on the required activation energy and the difference in free energies. However since small-molecule drugs are flexible, there is no way to tell what a large floppy molecule can do in the solid state except by doing experiments. Generally experiments to find polymorphs reveal the more stable forms first rather than the less stable, metastable polymorph forms. However the ground state usually is the least soluble. Some polymorphs are more difficult to formulate than others because of shape or hygroscopicity, and the importance of ensuring that conversion from one form to another is extremely important (Rouhi, p. 31-32). The process of preparing a pharmaceutical composition will cause a specific crystalline form, if it is in a metastable state to convert back to the most thermodynamically stable form, which is the form with the lowest vapor pressure. This

could lead to the disappearance of a polymorph form or appearance of a new polymorph. Additionally an acceptable carrier for a pharmaceutical formulation can be water. Dissolving a specific crystalline form in water and forming an aqueous solution would cause the compound to exist in free form rather than a crystalline form with an identifying X-ray diffraction pattern. In such conditions, the use of a wrong polymorph of a drug could cause a phase conversion from the metastable to stable polymorph to occur (Haleblian *et al*, pg. 912).

The amount of direction or guidance present and the presence or absence of working examples

The specification describes a process for the use of a crystalline form of levorotatory cetirizine dihydrochloride salt and a crystalline form of dextrorotatory cetirizine dihydrochloride salt and generic processes for preparing pharmaceutical compositions, including possible excipients. However the specification fails to provide results or test data to show that any composition containing the claimed compounds, a crystalline form of levorotatory cetirizine dihydrochloride salt and a crystalline form of dextrorotatory cetirizine dihydrochloride salt, would retain the specifically claimed polymorphic forms and would not result in the conversion to another polymorph, such as the most thermodynamically stable form or the free form of the compound, after a solvent such as water is added. Although the specification discloses methods as to how the claimed polymorphic forms of levorotatory cetirizine dihydrochloride salt and dextrorotatory cetirizine dihydrochloride salt can be detected in a composition, there are no actual examples that show these particular polymorphs are retained when added to

any excipient. The exemplified granules contain the amorphous dihydrochloride salt of cetirizine (see p. 21 of specification) and not the claimed polymorphic forms.

The breadth of the claims

The instant breadth of the rejected claim is broader than the disclosure, specifically, the instant claims include a pharmaceutical composition made with an excipient and a crystalline form of levorotatory cetirizine dihydrochloride salt and a crystalline form of dextrorotatry cetirizine dihydrochloride salt but fails to disclose if the composition would actually still contain the specific polymorphic form of levorotatry cetirizine dihydrochloride salt and dextrorotatry cetirizine dihydrochloride salt after pharmaceutical preparation of if a different form would appear.

The quantity or experimentation needed and the level of skill in the art

While the level of skill in the art is high, one of ordinary skill in the art would be unable to predict or maintain a specific crystalline form in a composition upon its preparation without experimental direction and guidance. The unpredictability of the existence of polymorphic forms of a chemical compound, and the interconversion from one metastable form to another stable form under ordinary conditions would cause undue experimentation for one to ascertain what would be contained in the composition, and the exact conditions for its preparation. Furthermore, through the process of adding excipients such as water or the process of wet milling, the claimed polymorphic form of the compound could change so that the particular form is no longer found in the composition. In view of the breadth of the claim, the chemical nature of the invention and unpredictability of formulating a composition with a crystalline structure of a

compound, and the lack of working examples regarding the activity as claimed, one skilled in the art would have to undergo an undue amount of experimentation to make the instantly claimed invention commensurate in cope with the claims. Absent factual data to the contrary, claims 6-7 and 22-23 are rejected under 35 U.S.C. § 112, 1st paragraph.

New Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 7, 19 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The nature of the invention is levorotatory 1-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride and dextrorotatory 1-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride. The state of the prior art is that the most useful method to compare X-ray powder diffraction data is to overlay and align the respective films or plots. The ensuing comparisons of peak positions and intensities will show whether the structures are the same or different (Byrn page 63). An x-ray diffraction pattern is like a "fingerprint" and applicant has not provided why the certain peaks found in the claims are the only required peaks in the x-ray diffraction pattern that

must match. The peaks present in the claims 3, 7, 19 and 23 do not include all peaks of the x-ray diffraction pattern, nor does the specification provide any direction or guidance as to why certain peaks are the only required peaks in the x-ray data or other data. The claims 3, 7, 19 and 23 are only drawn to certain peaks which is not the entire "fingerprint". The amount of direction present in the specification are the x-rays of levorotatory 1-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride and dextrorotatory 1-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride. Page 9 discloses the data for levorotatory 1-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride and dextrorotatory 1-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride. Applicant has not provided why the entire "fingerprint" is not being claimed, nor does applicant provide why only certain peaks are found in the claims and not others. The claims to only certain peaks do not find written description in the specification as the claims do not include the enter "fingerprint" and the specification fails to provide any description as to why the data claimed is characteristic of levorotatory 1-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride and dextrorotatory 1-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride and why the entire "fingerprint" is not required. Therefore the claims 3, 7, 19 and 23 are rejected as there is no written description as to why the data present is the only data required from the "fingerprints" to distinguish levorotatory 1-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride and dextrorotatory 1-[(4-

chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride from other forms.

New Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "effective amount" is indefinite where the claim fails to state the function which is to be rendered effective. See In re Frederiksen, 102 USPQ 35 (CCPA 1954).

New Prior Art Rejections

In regards to applicants compound claims 2-5 and 18-21, the prior art references of UK Patent Application 2,225,321 while not providing applicants' instant X-ray diffraction data, do disclose levorotatory 1-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride (p. 8) and dextrorotatory 1-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride (p. 9) in crystalline form, which puts these products in the public domain. As these forms differ from the claims in that the references are silent on the crystalline form, applicant must show that their crystalline form really is different from any of the ones prepared in the prior art. MPEP 2112 states: "Something which is old does not become patentable upon the discovery of a new property. The claiming of a new use, new function or unknown property, which is inherently present in the prior art does not necessarily make the claim

patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430,433 (CCPA 1977)." In this case, the "unknown property" is the particular crystalline form. This is unknown because the references are silent on this property.

This is not an ordinary inherency situation where it is not explicitly stated what the product actually is. Here the reference explicitly teaches exactly what the compound is. The only difference is a characteristic about which the reference happens to be silent. See also Ex parte Anderson, 21 USPQ 2nd 1241 and 1251, discussion of Rejection E. There, the decision states, "There is ample precedent for shifting the burden to an applicant to reproduce a prior art product whose final structure or properties are, at least, in part determined by the precise process used in its manufacture." (page 1253). The "properties' branch of that statement applies here. Applicants are reminded that the PTO has no testing facilities. It is noted that the composition claims 6-7 and 22-23 are rejected under 35 USC 102 as the prior art reference discloses that the dihydrochloride salt of cetirizine is found in medicaments (i.e. pharmaceutical compositions) comprising applicants' instantly claimed invention. It is the state of the prior art that the preparation of pharmaceutical compositions requires milling, adding excipients, surfactants, etc. The process of preparing a pharmaceutical composition will cause a specific crystalline form, if in the metastable state, to resort back to the most thermodynamically stable form, which is the form with the lowest vapor pressure. Polymorphs tend to convert from less stable to more stable forms (Rouhi, page 32). Thus, the same polymorphic form would be found in the prior art composition as the instantly claimed composition.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2-5 and 18-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Cossement *et al.*, UK Patent Application 2,225,321. Cossement *et al* teach the crystalline levorotatory and dextrorotatory dihydrochloride salt of cetirizine. See p. 8-10.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Cheng whose telephone number is 571-272-6233. The examiner can normally be reached on M-F, 9AM to 5:30PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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